Medical Staff Conference

Diet and Cancer—Should We Change What We Eat?

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD:* *Our speaker for this conference is Dr Sue Desmond. A graduate of the University of Nevada School of Medicine, she is completing her house-staff training on the medical service at the University of California, San Francisco, serving during this past year as an outstanding Chief Resident at Moffitt Hospital. Her future plans include fellowship training in hematology and oncology. She has chosen a particularly provocative title to discuss, "Diet and Cancer—Should We Change What We Eat?"*

SUSAN DESMOND, MD:† In the May 8, 1986, issue of *The New England Journal of Medicine*, an article entitled "Progress Against Cancer?" attempted to address the overall progress against this disease during the years 1950 to 1982.[1] In 1962 a total of 278,562 Americans died of cancer, a figure that increased by 56% to 433,795 American deaths from cancer in 1982. Even when adjusted for population growth and aging, this figure represents an increase of 8.7%. Incidence rates of all cancers are up in both white women and white men, a fact that suggests a failure to control new cases of cancer. Mortality data are especially striking for increases in deaths from lung cancer, a clear-cut environmentally associated tumor. There has been an apparent increase in mortality from breast cancer among white and nonwhite women since 1950, and mortality from cancer of the prostate in men has not changed appreciably. Mortality from stomach cancer has decreased due to decreases in incidence, and colon cancer has also declined in mortality. The authors' interpretation of these data is that "large monetary expenditures have led to increases in our understanding of cancer, but not to decreases in incidence or mortality."[1] Their conclusion is that a refocusing of our efforts from treatment to prevention is in order.

Cancer and the Environment

It has been estimated that as many as 80% to 90% of all human cancers are attributable to environmental influences and are therefore preventable.[2] This statement is based on the assumption that the lowest rate for each type of malignancy identified in worldwide surveys represents the "natural incidence" of the disease and that environmental factors contribute to the higher rates found elsewhere. For example, the United States has an overall incidence rate of cancer in men approximately 90% higher than that in Honduras, which has the lowest international incidence. The excess deaths could result from environmental factors specific to the United States. There are problems with interpreting data such as these, however, with a large number of "confounding variables," probably the most important being the age structure of the various populations and the completeness with which the causes of death are determined and reported. In the example cited, Honduran men had a 1974 life expectancy of 52 years versus 68 years for American men, an especially important confounding variable because 80% or more of cancer deaths in the United States occur after the age of 55.

Even more striking than international differences in overall cancer rates are those found in site-specific categories in which, for commonly affected sites, tenfold to thirtyfold differences are seen. For example, if one compares the cancer incidence in Bulawayo, Zimbabwe (formerly Rhodesia), and Geneva, Switzerland, liver cancer rates are higher in both men and women in Bulawayo, whereas the rates in Geneva for colon and breast cancer far exceed the Bulawayo rates. In fact, female breast cancer rates in Geneva are five times greater than those seen in Bulawayo. Such pronounced international variations in site-specific cancer rates contain important clues for understanding the etiology of human cancer.[3]

In the past, country-to-country variations in cancer incidence were often attributed to racial or genetic factors. Today most authors agree that these factors account for only a small minority of cancers, with genetic factors directly responsible for no more than 2% of all human cancers. In recent years, the results of studies of migrant populations have severely undermined the concept of racially or genetically based carcinogenesis. Migrant populations basically exchange one environment and its carcinogenic risks for another and its risks.

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Because the genetic endowment remains the same in both environments, any large variations from cancer rates in the country of origin are best explained in terms of differences in environmental exposure. Almost all migrant studies have had the same findings: cancer patterns in migrants tend to approximate those in the adopted country and differ from the country of origin.

Cigarette smoking is the best identified environmental factor associated with cancer; other carcinogenic agents include radiation and chemicals (usually occupational exposures) and viruses (a general exposure). With the exception of smoking and occupational hazards, nutrition is probably the most important environmental risk.

In 1984 the American Cancer Society published a list of seven dietary recommendations for avoiding cancer (Table 1). These include both avoiding certain foods, such as fats, and including other foods in the diet, such as cruciferous vegetables.[4]

Obesity and Cancer

The observation that one should avoid obesity to decrease cancer risk comes from both experimental and epidemiologic evidence. It has long been known that laboratory animals fed a low-caloric diet showed a decrease in chemically induced tumors, but that high-caloric diets often were high in fats, so that the effects of calories were difficult to separate from those of fats.[5] When mice are given gold thioglucose, however, which induces obesity via a specific hypothalamic lesion, there is a higher incidence of mammary tumors, so obesity itself may increase tumor formation.[6]

The American Cancer Society did a long-term prospective study over the period 1959 to 1972, drawing 750,000 men and women from the general population.[7] The lowest mortality rates were found in those close to average weight and those 10% to 20% below average weight. Mortality among men and women 30% to 40% heavier than average weight was nearly 50% higher than those of average weight. Excess cancer mortality in obese persons was seen mainly in women, who had more cancers of the gallbladder, breast, cervix, endometrium and ovaries.

Dietary Carcinogens

One very noticeable feature of the American Cancer Society's recommendations is a lack of great emphasis on "carcinogens" in the diet. In fact, only with their final recommendation to decrease the intake of smoked and cured foods (because of their links to gastric and esophageal cancer) is this concept addressed. Contrary to what was thought 20 to 30 years ago, food additives and contaminants have not, with the exception of aflatoxin, proved very important in human cancers. Since the early 1970s there has been a shift in emphasis to general food types in the diet and how they affect our cancer risk.

Advances in analytic technology, especially the Ames test, have disclosed that in experimental systems an astonishing variety of compounds occurring naturally in the diet are carcinogenic or mutagenic.[8] Such commonly consumed foodstuffs as celery, rhubarb, cocoa powder, tea, mustard, lettuce and spinach contain potential mutagens or carcinogens. Ames concluded, "Nature is not benign; no human diet can be entirely free of mutagens and carcinogens."[8] In fact, the very low concentrations at which most carcinogenic substances occur and the large number of anticarcinogens found in the diet minimize the overall hazard to humans.

TABLE 1.—*Dietary Recommendations of the American Cancer Society*

Avoid obesity
Cut down on total fat intake
Eat more high-fiber foods, such as whole grain cereals, fruits and vegetables
Include foods rich in vitamins A and C in the daily diet
Include cruciferous vegetables, such as cabbage, broccoli, brussels sprouts, kohlrabi and cauliflower in the diet
Be moderate in the consumption of alcoholic beverages
Be moderate in the consumption of salt-cured, smoked and nitrite-cured foods

Dietary Fats and Cancer

In the 1982 report of the National Research Council concerning diet, nutrition and cancer, fats were singled out as the factors for which the strongest association with cancer had been made.[9] Unsaturated fats contain one, two or more double bonds, and their usual source is vegetable oils such as safflower oil. Saturated fats, with no double bonds, are largely animal products (with notable exceptions such as coconut oil); examples include beef, butter, cheese and chocolate. It is of note that in the period 1963 to 1977, Americans decreased their intake of animal fats and oils by 47%, but increased their intake of vegetable fats and oils by 58%.

A large amount of experimental evidence has accumulated regarding dietary fats and cancer. The mouse mammary tumor system has been studied most extensively.[10] The incidence of tumors induced by chemicals or arising spontaneously in this system is increased by a high-fat diet, even with careful control of caloric intake by using isocaloric diets.

This experimental finding has been confirmed in numerous subsequent studies. In both rats and mice and with both spontaneous and induced mammary tumors, the animals fed a high-fat diet have more tumors, with earlier appearance of the tumors and more tumors per animal.[11] Given at high levels, polyunsaturated fats result in more tumor formation than do saturated fats.[12] The total amount of fat appears to be more important than the type of fat, as long as the animals are given a small supply of dietary essential fatty acids along with high amounts of dietary fat.[13,14]

The experimental data concerning fat and cancer are of greater interest because of epidemiologic evidence showing a strong positive correlation between the total amount of dietary fat available for consumption and the age-adjusted death rate from breast cancer.[15] A major problem with information of this type is that countries with a low incidence of breast cancer tend to be relatively underdeveloped, such that any variable related to economic development is likely also to be related to breast cancer incidence—indeed, there is also a linear correlation between the gross national product and the incidence of breast cancer.

For the period 1968 to 1972, the annual age-adjusted incidence of breast cancer in Miyagi, Japan, was 13 per 100,000, while the corresponding figure for Connecticut was 71.4 per 100,000. The risk in the US city was 5.5 times higher than that in Japan and increased to 8 times higher if

only postmenopausal women were studied. In two different surveys carried out in 1968 and 1969, Americans were found to consume three times the amount of fat as did the Japanese.[16]

The incidence of breast cancer has recently been increasing in Japan, with a doubling of mortality rates from this disease from 1955 to 1975. Surveys of various districts in Japan showed that the incidence in breast cancer rates correlated with those districts where fat intake had increased. In the 1950s to the 1970s there was an increasing westernization of the Japanese diet, with increased fat intake, increasing weight and an earlier onset of menarche.[17,18]

Several different mechanisms have been proposed for the relationship between dietary fat and breast cancer. These include hormonally mediated changes, fat-induced obesity itself, changes in immune response and changes in membrane properties. Hormonal changes have been studied in this regard.[19] In rats the enhancing effect of dietary fat appears to be mediated via prolactin,[20] but there has been no convincing evidence for a role of prolactin in humans. Estrogens assume particular importance in the current concepts of the possible role of obesity in postmenopausal breast cancer. Postmenopausal circulating estrogens are largely derived from the aromatization of androstenedione, resulting in the formation of the estrogen estrone. The principal site for this conversion is adipose tissue, and the composition of adipose tissue depends in part on the diet. The older and more obese a woman is, the greater her peripheral estrogen formation.[21] Studies looking at hormone levels in patients with breast cancer have had mixed results. Recently investigators have begun to measure hormone levels in breast secretions.

Dietary Fiber and Cancer

Of all areas of interest in this field, the one receiving the most media attention is the fiber hypothesis. One needs only to read the back of the morning cereal box to get the latest information from the National Cancer Institute on diet and cancer. Interest in the relationship between dietary fiber and large bowel cancer is largely the result of Dennis Burkitt's observation of low colon cancer rates in areas of Africa where fiber consumption and stool bulk are high.[22] Burkitt proposed that a high-fiber diet would effectively dilute out carcinogens. He found that African villagers had a stool bulk about four times that of English boarding-school pupils. The finding of increased stool bulk with high-fiber diets has since been confirmed by other authors and is thought to be due to indigestible fibers contributing directly to stool bulk as well as water adsorbed onto the fiber.

Burkitt and co-workers also proposed that diets low in fiber lead to a slow transmission of dietary components through the gut. The slow transit time may allow a longer time during which carcinogens present in the gut may be in contact with the gut wall.[23] The concept of a decreased transit time due to fiber intake has been questioned. Studies have shown that patients with a stool transit time of a day or less (comparable to the irritable bowel syndrome) actually have a longer transit time when fiber is added to their diet. Other aspects of Burkitt's fiber hypothesis have also been questioned, especially his emphasis on cereal fiber. African diets are actually low in cereal fiber, with most of their intake consisting of fruits and vegetables.[24] Also, despite the emphasis on the fiber they contain, fruits and vegetables are high in vitamins A and C, as well as other substances that may exert a protective effect.

One problem with interpreting the dietary fiber data is the wide variety of fiber types termed "dietary fiber," some more digestible than others. There are two major classes of fiber: polysaccharides and lignins. The most digestible fiber types are those found in fruits and vegetables; the least digestible are lignins, which are mainly found in cereal brans.

Results of experimental studies of the effect of fiber on colon carcinogenesis have been mixed, largely because of major differences in the fiber used in different animal species.[25] Epidemiologic studies have also been inconclusive. Fiber intake is generally higher in countries with a low incidence of colon cancer, but studies done in Canada, Puerto Rico and Hong Kong showed no protective effect of fiber. The protective effect is more readily seen in populations with a high fat intake, as in studies comparing the diet of rural Scandinavians (high fat, high fiber) with that of New Yorkers (high fat, low fiber) in which the latter had a higher colon cancer rate.[26] In one study done of American blacks in the San Francisco Bay Area, the relative risk of colon cancer among blacks with a low-fiber, high-fat diet was 2.68 times greater than in blacks with a high-fiber, low-fat diet.[27] Overall, epidemiologic evidence to date suggests that dietary fiber plays a role in protecting the colon against carcinogens, but that other factors may be equally or more important.

Dietary fats are thought to play an important role in colon cancer etiology. Epidemiologic correlations can be made between the amount of dietary fat available for consumption and colon cancer rates. Countries with a high rate of breast cancer commonly have higher rates of colon cancer as well. Experimental evidence suggests that rodents fed a high-fat diet have increases in colon cancers induced by various carcinogens. Unfortunately, many of these studies did not control for caloric intake.[28]

How do changes in diet affect colon cancer incidence? Primary and secondary bile acids are thought to play a role in colon carcinogenesis, not as inducers, but as promoters. The theoretic basis for the carcinogenic activity of the bile acids is their structural similarity to such hydrocarbons as methylcholanthrene, a known potent carcinogen, and the possibility of bacterial conversion of bile acids to carcinogenic compounds. The yield of chemically induced colon cancers in rats is significantly increased when bile acids are given intrarectally.[29] Bile acids alone produce no tumors, suggesting that the bile acids produce their effects as promoters. In the animal model, the carcinogenic effects of azoxymethane are increased by surgically diverting bile to the middle of the intestine, a procedure that increases fecal bile acids. An increase in fat in the duodenum is known to stimulate bile acid release, and a western diet has been linked to an increase in the fecal content of bile acids. A diet high in fat and low in fiber may also change gut flora towards more anaerobic bacteria that are better able to convert primary to secondary bile acids and are postulated to change bile acids to carcinogenic compounds.

Dietary Cholesterol and Cancer

Cholesterol is the obligate precursor of bile acids, a fact that is of greater significance in light of recent studies on cholesterol and cancer. Population studies have shown a strong positive correlation between the per capita consump-

tion of cholesterol and regional differences in colon cancer rates. Also, international rates of coronary artery disease mortality (linked to a high-cholesterol diet) are seen to be high in areas with high rates of colon cancer. Animal studies have shown cholesterol to be a potent dietary cocarcinogen.[30] Despite these facts, at least eight studies have shown a statistically significant inverse association between blood cholesterol levels and total cancer mortality, especially at cholesterol levels of less than 190 mg per dl.[31] Virtually all of the evidence relating blood cholesterol to the subsequent development of cancer is drawn from long-term prospective cohort studies in which cardiovascular disease was the end point of principal interest. One of the key questions is whether the inverse relationship reported in some of these studies could be due to the fact that these cohorts had persons with cancer at the time of entry, with already depressed cholesterol levels due to their cancer. If one eliminates persons who died within the first two years of their base-line studies, the inverse relationship persists in three studies—that is, a low serum cholesterol level associated with a subsequent higher cancer death rate. Not all published studies have shown such a relationship; in eight studies there was no relationship between a low serum cholesterol level and increased cancer mortality, and, in fact, two showed a trend toward a positive relationship.

An apparent paradox is raised by these data: the evidence from some prospective studies points to a possibly harmful effect of a low serum cholesterol level, yet the studies of diet point to a relationship between an increased intake of cholesterol and an increased cancer risk. It has been hypothesized that the relationship of cholesterol intake to cancer is found in a subgroup of the population with a high intake but low blood levels due to increased excretion of cholesterol.[32] An effort to reduce serum cholesterol levels by the use of clofibrate led to the unexpected result of a 25% higher mortality in the clofibrate group than in controls. A small part of this increase was due to more cancer deaths in the clofibrate group. Although not statistically significant, the 11 colon cancer deaths in the clofibrate group versus 6 in the controls raises a concern about a potentially harmful effect of exposing the colon to higher amounts of cholesterol.[33] Supplementing the diet with large amounts of polyunsaturated fats in rats caused a shift of cholesterol from the systemic circulation to the gut lumen and an increase in large bowel tumors.[34] It is clear that the cholesterol-cancer relationship is a complex one. Future studies should be done with a look not only at serum cholesterol levels, but at cholesterol excretion as well.

Cruciferous Vegetables and Cancer

In an attempt to better understand the relationship between diet and colon cancer, a large number of dietary surveys have been done. In spite of the many differences in design and method of selecting controls, several studies of diet reported by patients with colon cancer suggest a protective effect of vegetables. In addition to containing fiber and vitamins A and C, vegetables are also known to contain materials that are capable of inhibiting experimentally induced tumor formation. Human cells, especially hepatocytes, are well adapted to detoxify foreign compounds and to produce excretable metabolites. One prominent example is the mixed-function oxidase system, which has the ability to detoxify many of the known carcinogens. In nature there are numerous compounds with the capacity to induce the activity of these detoxifying systems and to inhibit experimental carcinogenesis.[35]

One of the best studied examples of this inducer phenomenon is seen in the vegetables of the Brassicaceae family, such as brussels sprouts, cabbage, cauliflower and broccoli. These vegetables contain large amounts of indoles, which are known to induce increased activity of the mixed-function oxidase system that breaks down polycyclic aromatic hydrocarbons. Studies of animals have shown that increases in this activity can protect against neoplasia induced by hydrocarbons.[36]

Vitamins, Minerals and Cancer

The American Cancer Society recommends including foods rich in vitamins A and C in the diet, a recommendation that is derived from recent work done in the area of "chemoprevention." Chemoprevention is a rapidly growing area of research based on the concept that the public is more likely to accept prescription than proscription—that is, would rather add to the diet than to take away. In addition to vitamins A and C, vitamin E and the trace mineral selenium are thought to have potential roles in preventing cancer.

As seen in Table 2, the "conservative" recommendations for cancer prevention involve ingesting doses higher than the recommended daily allowance of these substances, an important fact, as each is potentially harmful at very high doses.[37] Preformed vitamin A is found in liver, butter, whole milk, cheese and egg yolk, and vitamin A's precursor β-carotene is found in green and yellow vegetables. Although a sustained high intake of β-carotene leads only to reversible skin discoloration, long-term doses of vitamin A of more than 25,000 IU per day result in significant toxicity, which may include exfoliative dermatitis, dry mucous membranes, headaches, emotional lability, fatigue, epistaxis, edema and liver function abnormalities with hepatomegaly. Vitamin E is the least toxic of the fat-soluble vitamins, but doses of higher than 1,200 IU per day are reported to cause nausea, diarrhea, intestinal cramps, skin reactions, myopathy and gonadal dysfunction. Although most patients taking high doses of vitamin C have no side effects, doses of 2 to 10 grams or more daily may result in acidosis, oxaluria, diarrhea and nephrolithiasis. Like vitamin A, selenium at high doses can lead to serious and irreversible side effects, including multiple dermatologic abnormalities and peripheral nervous system dysfunction.

Oxygen-free radicals are thought to be a common mechanism through which many carcinogens act. Vitamins C and E, β-carotene and selenium are all known to protect against free radical damage.[38] In addition, vitamins C and E inhibit nitrosamine formation. The role of vitamin E in preventing human cancers is largely unexplored, and the modifying effects of vitamin E in animals treated experimentally with carcinogens have been variable. Much more work has been done with vitamin C, with protective effects seen in human stomach, esophageal and laryngeal cancers, as well as cervical dysplasia. Linus Pauling and others have examined the possible role of vitamin C in extending survival in advanced cancer. In a series of 100 cases compared with 1,000 historical controls drawn from a review of records, they claimed a striking survival advantage in their patients given 10 grams of vitamin C daily.[39] This work has been questioned, and recent double-blind, randomized studies done at the Mayo Clinic

TABLE 2.—*Dietary Intake of Vitamins A, E and C and Selenium in Preventing Cancer**

Nutrient	RDA	Conservative Recommendation for Cancer Prevention	Serum Levels of Possible Toxicity
Vitamin A, IU	5,000	12,500	Limited: long-term intake 25,000/d; short-term intake 300,000-1,000,000
Vitamin E, IU	10-20	200-800	Negligible: 1,200
Vitamin C, mg	60	1,000	Negligible: 1,000-2,000
Selenium, μg	None	50-200	Significant: 200

RDA = recommended daily allowance

*Adapted from Watson and Leonard.[37]

have shown no prolongation of survival in patients with advanced cancer given the same dosages of vitamin C.[40]

Selenium, an essential trace element, has a key role in the activity of the enzyme glutathione peroxidase, which protects against oxidative damage to cells. Both internationally and in the United States, geographic areas with low selenium levels in the soil or in blood specimens have higher cancer rates than in high-selenium areas; the strongest inverse relationships are seen with breast and colon cancer. These data should be interpreted cautiously, however, as high selenium levels in soil tend to occur in more rural areas, and variables other than selenium may be more important. Experimental evidence, however, points to a possible anticarcinogen role for selenium. In tissue cultures, selenium reduces the metabolic activation of certain carcinogens, altering the pattern of degradation to less toxic metabolites. In a large number of animal experiments, using a wide variety of inducing agents, selenium-supplemented animals have had tumor incidences approximately half those of control animals.[41] Overall, selenium remains an intriguing possible chemopreventive agent, but toxicity currently limits its use to the experimental setting.

Some of the most exciting research in the area of chemoprevention has been done with the retinoids. The precursor of vitamin A is β-carotene, the major carotene in the diet. β-Carotene can be oxidized to the aldehyde retinal, then to the alcohol retinol. Naturally occurring retinols are toxic in humans if ingested in high doses, so that a number of retinol analogues have been studied, especially all-*trans*-retinoic acid, 13-*cis*-retinoic acid and etritinate.

The results of many epidemiologic surveys imply that there is an inverse relationship between some forms of cancer and the intake of β-carotene as well as of retinol. Possibly β-carotene itself exerts a protective effect, as it is known to be a potent free radical scavenger.[42] Studies have shown that a matched population with a lower consumption of vitamin A had an increased incidence of lung cancer. This type of study has also shown positive results in patients with esophageal, laryngeal and bladder carcinoma. Other data, such as those from the Hypertension Detection and Follow-up Program, have failed to show a relationship between retinol and retinol-binding protein and the subsequent development of malignancy over the next five years.[43] Possibly the most important question of all concerns the issue of cancer prophylaxis with vitamin A analogues in the general population. The National Cancer Institute is currently funding about 16 studies of the use of vitamin A analogues or β-carotene in either the general population or in high-risk groups to test a possible lowering of cancer mortality.

TABLE 3.—*Overview of Diet's Role in Cancer*

- Diet may be a factor in as many as 35% of all cancers
- No diet is free of all known mutagens and carcinogens
- Intake of dietary fats, both saturated and unsaturated, should be decreased from America's current level of 40% of caloric intake
- Dietary fiber probably plays a role in protecting the colon against carcinogenic challenges, but other factors may be equally or more important
- Diets should contain foods high in vitamins A and C and in cruciferous vegetables, but vitamin supplements should be used with caution

Regardless of the outcomes of these studies, it is clear that study of the relationship of vitamin A and cancer on an experimental level can teach us something about the basic processes of carcinogenesis.[44]

Retinoids are potent agents for controlling cellular differentiation and proliferation. Data gathered from animals exposed to carcinogens or from carcinogens added in tissue culture systems almost universally support a preventive role for vitamin A and other retinoids in cancer development. Vitamin A deficiency produces squamous metaplasia; excess vitamin A leads to mucous metaplasia in previously normal keratinized squamous epithelium. The premalignant phenotype of mouse prostate glands that have been treated with the carcinogen 3-methylcholanthrene can be altered by retinoids. The atypical epithelial cells that are induced by the carcinogen disappear on retinoid treatment of the organ cultures and are replaced by cells with more normal morphology.[45]

In cell culture studies, retinoids can be clearly shown to be suppressors of the malignant phenotype in cells previously treated with carcinogens. Removing the retinoids allows expression of the transformed state. Even more promising, retinoids can change the differentiation of invasive neoplastic cells growing in culture. For example, in the human promyelocytic leukemia system, retinoids can induce terminal differentiation of malignant leukemia cells, leading to formation of morphologically mature granulocytes, which have functional markers of mature neutrophils.[46] In summary, retinoids can suppress experimental carcinogenesis in vivo, can suppress development of the malignant phenotype in vitro and can even exert effects on some fully transformed and invasive neoplastic cells.

Conclusions

A cautious observer would conclude that more research in the area of diet and cancer is needed. If one looks at smoking and lung cancer as a model, however, it is reasonable to

change behaviors before all of the data are available, potentially changing the cancer risks for millions of people. Table 3 outlines several recommendations based on currently available data.

REFERENCES

1. Bailar JC, Smith EM: Progress against cancer? N Engl J Med 1986; 314: 1226-1232

2. Creasey WA: Diet and Cancer. Philadelphia, Lea & Febinger, 1985, pp 1-4

3. Higginson J: The face of cancer worldwide. Hosp Pract 1983; 18:145-149, 153-157

4. Nutrition and cancer: Cause and prevention—An American Cancer Society special report. CA 1984; 34:121-126

5. Tannenbaum A: Initiation and growth of tumors: Introduction: Effects of underfeeding. Am J Cancer 1940; 38:335-350

6. Waxler SH: Obesity and cancer susceptibility in mice. Am J Clin Nutr 1960; 8:760-766

7. Lew EA, Garfinkel L: Variations in mortality by weight among 750,000 men and women. J Chronic Dis 1979; 32:563-579

8. Ames BN: Dietary carcinogens and anticarcinogens. Science 1983; 221: 1256-1263

9. National Research Council: Diet, Nutrition, and Cancer. Washington, DC, National Academy Press, 1982

10. Tannenbaum A: The genesis and growth of tumors: III. Effects of a high-fat diet. Cancer Res 1942; 2:468-475

11. Carroll KK: Lipids and carcinogenesis. J Environ Pathol Toxicol Oncol 1980; 3:253-271

12. Carroll KK, Khor HT: Dietary fat in relation to tumorigenesis. Prog Biochem Pharmacol 1975; 10:308-353

13. Carroll KK, Hopkins GJ: Dietary polyunsaturated fat versus saturated fat in relation to mammary carcinogenesis. Lipids 1979; 14:155-158

14. Hopkins GJ, Carroll KK: Relationship between the amount and type of dietary fat in the promotion of mammary carcinogenesis induced by 7,12-dimethylbenz-anthracene. JNCI 1979; 62:1009-1012

15. Segi M, in collaboration with Noye H, Hattori H, Yazazaki Y, et al: Age-Adjusted Death Rates for Cancer of Selected Sites (A-Classification) in 52 Countries in 1973. Nagoya, Japan, Segi Institute of Cancer Epidemiology, 1978

16. Wynder EL, Rose DP: Diet and breast cancer. Hosp Pract [Off] 1984; 19:73-78, 83-88

17. Hirayama T: Epidemiology of breast cancer with special reference to the role of diet. Prev Med 1978; 7:173-175

18. Hirayama T: Changing patterns of cancer in Japan with special reference to the decrease in stomach cancer mortality, *In* Hiatt HH, Watson JD, Winsten JA (Eds): Origins of Human Cancer. Cold Spring Harbor, NY, Cold Spring Harbor Laboratory, 1977, pp 55-75

19. Rose DP: Diet, hormones, and breast cancer, *In* Endocrinology of Cancer. Boca Raton, Fla, CRC Press, 1982

20. Ip C, Yip P, Bernardis LL: Role of prolactin in the production of dimethylbenzanthracene-induced mammary tumors by dietary fat. Cancer Res 1980; 40:374-378

21. Kirschner MA, Schneider G, Ertel NH, et al: Obesity, androgens, estrogens, and cancer risk. Cancer Res 1982; 42(suppl):3281-3285

22. Burkitt DP: Epidemiology of cancer of the colon and rectum. Cancer 1971; 28:3-13

23. Burkitt DP, Walker ARP, Painter NS: Effect of dietary fibre on stools and transit times, and its role in the causation of disease. Lancet 1972; 2:1408-1411

24. Eastwood MA, Fisher N, Greenwood CT, et al: Perspectives on the bran hypothesis. Lancet 1974; 1:1029-1033

25. Kritchevsky D: Fiber, steroids, and cancer. Cancer Res 1983; 43(suppl): 2491S-2495S

26. Kritchevsky D: Dietary fiber and cancer. Nutr Cancer 1985; 6:213-219

27. Dales LG, Friedman GD, Ury HK, et al: A case-control study of relationships of diet and other traits to colorectal cancer in American Blacks. Am J Epidemiol 1979; 109:132-144

28. Kritchevsky D, Klurfeld DM: Fat and cancer, *In* Newell GR, Ellison NM (Eds): Nutrition and Cancer: Etiology and Treatment. New York, Raven Press, 1981

29. Reddy BS: Dietary lipids and their relationship to colon cancer, *In* Diet, Nutrition and Cancer: From Basic Research to Policy Implications. New York, Alan R. Liss, 1983

30. Cruse JP, Lewin R, Ferulano GP, et al: Co-carcinogenic effect of dietary cholesterol in experimental colon cancer. Nature 1978; 276:822-825

31. Fienleib M: Review of the epidemiologic evidence for a possible relationship between hypocholesterolemia and cancer. Cancer Res 1983; 43(suppl):2503S-2507S

32. Lowenfels AB: Is increased cholesterol excretion the link between low serum cholesterol and colon cancer? Nutr Cancer 1983; 4:280-284

33. A co-operative trial in the primary prevention of ischemic heart disease using clofibrate: Report from the committee of principal investigators. Br Heart J 1978; 40:1069-1118

34. Broitman SA, Vitale JJ, Varrousek-Jakuba E, et al: Polyunsaturated fat, cholesterol, and large bowel tumorigenesis. Cancer 1977; 40:2455-2463

35. Wattenberg LW, Loub WD, Lam LK, et al: Dietary constituents altering the responses to chemical carcinogens. Fed Proc 1976; 35:1327-1331

36. Wattenberg LW, Loub WD: Inhibition of polycyclic aromatic hydrocarbon-induced neoplasia by naturally occurring indoles. Cancer Res 1978; 38:1410-1413

37. Watson RR, Leonard TK: Selenium and vitamins A, E, and C: Nutrients with cancer prevention properties. J Am Diet Assoc 1986; 86:505-510

38. Cameron E, Pauling L: Supplemental ascorbate in the supportive treatment of cancer: Prolongation of survival times in terminal human cancer. Proc Natl Acad Sci USA 1976; 73:3685-3689

39. Moertel CG, Fleming TR, Creagan ET, et al: High-dose vitamin C versus placebo in the treatment of patients with advanced cancer who have had no prior chemotherapy—A randomized double-blind comparison. N Engl J Med 1985; 312:137-141

40. Shamberger RJ: Relationship of selenium to cancer—I. Inhibitory effect of selenium on carcinogenesis. JNCI 1970; 44:931-936

41. Kummet T, Moon TE, Meystens FL: Vitamin A: Evidence for its protective role in human cancer. Nutr Cancer 1983; 5:96-106

42. Peto R, Doll R, Buckley JD, et al: Can dietary beta-carotene materially reduce human cancer rates? Nature 1981; 290:201-208

43. Willett WC, Polk BF, Underwood BA, et al: Relation of serum vitamins A and E and carotenoids to the risk of cancer. N Engl J Med 1984; 310:430-434

44. Sporn MB, Roberts AB: Role of retinoids in differentiation and carcinogenesis. Cancer Res 1983; 43:3034-3040

45. Lasnitzki I: The influence of a hyper-vitaminosis on the effect of 20-methylcholanthrone on mouse prostate glands grown in vitro. Br J Cancer 1955; 9:438-439

46. Breitman TR, Collins SJ, Keene BR: Terminal differentiation of human promyelocytic leukemia cells in primary culture in response to retinoic acid. Blood 1981; 57:1000-1004